REMARKS

The Office Action dated August 5, 2009, has been received and carefully noted. The following remarks are being submitted as a full and complete response thereto.

Claims 1-26 and 28-31 are pending in this application, with claims 1, 23, and 29-31 being independent. By this Amendment, claims 1-26 and 28-31 have been amended, and claim 27 has been cancelled without prejudice to or disclaimer of the subject matter contained therein. Applicants submit that no new matter has been presented herein.

Applicants respectfully request reconsideration and withdrawal of the outstanding rejections.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 10-14 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement based on the use of the phrase "and derivatives thereof" in the claims.

Applicants respectfully traverse this rejection.

However, without conceding the propriety of this rejection, and in order to advance the prosecution of this application, Applicants have removed all instances of the phrase "and derivatives thereof" from the claims.

In view of the amendments and remarks set forth above, Applicants submit that the presently-claimed invention is fully supported by the written description provided in the specification, and respectfully request withdrawal of the rejection of claims 10-14 under 35 U.S.C. § 112, first paragraph.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1-31 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The reasons for this rejection are set forth on pages 3-6 of the Office Action, along with suggestions for overcoming the rejection.

Claims 1-26 and 28-31 have been amended to attend to various formalities, and claim 27 has been cancelled.

Further, Applicants submit the following comments.

Claims 1 and 29-31 have been amended to recite that the inventive compositions may be dispersible ***or*** orodispersible. The Office Action took the position that "orodispersible" is narrower than "dispersible" as used to describe the presently-claimed dosage forms, and the presence of both terms in the claim was considered indefinite. Applicants respectfully traverse this position. On page 4 of their specification, Applicants describe "dispersible" dosage forms that may be film coated or non-film coated, where the dosage forms are adapted to be dispersed in water prior to administration. By contrast, "orodispersible" dosage forms are described as non-film coated dosage forms that are adapted to be placed in the mouth, where they quickly disperse. Applicants have amended claims 1 and 29-31 to clarify that both dosage forms are encompassed by the presently-claimed invention.

Claim 10 has been amended to recite that the inventive compositions may comprise a PPAR gamma agonist, and the term "glitazone" has been removed.

Applicants submit that it is known in the art that PPAR gamma agonists are commonly referred to as glitazones.

Claim 11 has been amended to recite that the inventive compositions may comprise a PPAR gamma and alpha agonist, and the term "glitazar" has been removed. Applicants submit that it is known in the art that PPAR gamma and alpha agonists are commonly referred to as glitazars.

In view of the amendments and remarks set forth above, Applicants respectfully request withdrawal of the rejection of claims 1-26 and 28-31 under 35 U.S.C. § 112, second paragraph.

Rejection Under 35 U.S.C. § 103(a)

Claims 1-28 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 6,031,004 to Timmins et al. (hereinafter, "Timmins") and U.S. Published Appl. No. 2003/0139434 of Balkan et al. (hereinafter, "Balkan"), as evidenced by the W.S. Tyler product and price catalog (hereinafter, "Tyler"). Applicants respectfully traverse this rejection.

Timmins is cited for allegedly disclosing salts of the anti-diabetic agent metformin, including metformin fumarate and metformin succinate, which may be employed alone or in combination with another anti-hyperglycemic agent (*see* Abstract). Timmins discloses that the dosage form may be a tablet or capsule, among others (*see* column 4, lines 49-52). Timmins further discloses that the dosage forms may include from about 1% to about 80% excipients, such as lactose, sugar, corn starch, modified corn starch, mannitol, sorbitol, calcium carbonate, and microcrystalline cellulose (*see*

column 5, lines 8-12); one or more binders such as polyvinylpyrrolidone (having a molecular weight of preferably about 40,000), lactose, starches and polyethylene, among others (*see* column 5, lines 15-23); about 2% to about 8% by weight of disintegrants, such as croscarmellose sodium, crospovidone/cross-linked polyvinyl pyrrolidone, sodium starch glycolate, corn starch and microcrystalline cellulose (*see* column 5, lines 24-30); other excipients such as preservatives, silicon dioxide, and polymeric celluloses (*see* column 5, lines 34-46); and the sweetening agent xylitol, and the flavoring agents grape flavor, spice flavor and raspberry flavor (*see* column 10, lines 1-35).

In Example 4, Timmins discloses a tablet formulation containing the active agent metformin succinate in an amount of 80% (600/748x100), the binder hydroxypropylmethyl cellulose in an amount of 2% (15/748x100), the disintegrant croscarmellose sodium in an amount of 6% (45/748x100), the filler/diluting agent microcrystalline cellulose in an amount of 10% (80/748x100), and the additional excipient magnesium stearate. Timmins further discloses that the formulation of Example 4 is prepared by wet granulation, and includes the steps of mixing, granulating, drying and compressing into tablets (*see* column 7, lines 45-60).

Timmins also discloses that additional active ingredients may be included, such as pioglitazone (*see* column 3, line 64), thiazolidinedione/glitazone (*see* column 4, line 2), glimepride, glipyride, glipizide, chlorpropamide, glicazide and acarbose (*see* column 4, lines 24-26).

Regarding the size of the granules, the Office Action indicates that Timmins discloses that the mixtures of ingredients are passed through a #12 to #40 mesh screen

(6:3), which according to Tyler indicates a size of from 425 microns to 1.7 mm (*see* Tyler, page 3, table columns 1-2). However, this statement is inaccurate, for reasons that Applicants will discuss below.

The Office Action admits that Timmins does not disclose compositions that include a dipeptidyl peptidase inhibitor and/or a sugar coating. However, Balkan is cited for allegedly disclosing these features.

Balkan is cited for disclosing combination pharmaceutical compositions which include dipeptidyl peptidase four (DPP-IV) inhibitors and at least one anti-diabetic compound (*see* Abstract). Balkan further discloses compositions containing the anti-diabetic compound metformin, among others (*see* [0150]). Balkan further discloses the combination comprising DPP728 plus metformin (*see* [0175]). Balkan further discloses pharmaceutical preparations that are prepared by conventional mixing, granulating, and sugar-coating (*see* [0190]). Balkan further discloses that, if desired, the mixture may be processed to form granules, tablets, or sugar-coated tablet cores (*see* [0190]).

The Office Action takes the position that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine a DPP-IV inhibitor with a metformin pharmaceutical composition, as suggested by Balkan, because Timmins suggests the use of metformin in combination with other anti-diabetic drugs, and because Balkan discloses that DPP-IV inhibitors are anti-diabetic drugs suitable for use with metformin. The Office Action asserts that one of ordinary skill in the art would have been motivated to combine Balkan with Timmins because the resulting formulation would have increased efficacy due to the combination of the two anti-diabetic drugs. The Office Action further asserts that it would also have been

obvious to produce a sweetener-coated formulation because the sweetener would have a more appealing taste for the user, and would therefore increase patient compliance.

Applicants respectfully disagree with the positions taken in the Office Action.

The presently-claimed invention was developed in order to address the problem of preparing oral dosage forms containing metformin, which is difficult to work with because of its low compressibility, and low binding capability. These issues result in dosage forms that have an unacceptably large size. Further, even when the issue of the size of the dosage form is overcome, there are still problems associated with the trade-offs between providing acceptable mechanical properties to the dosage form and preserving its physical integrity during storage, and the ability of such dosage forms to dissolve quickly on contact with an aqueous solution. Attempts to solve this problem by providing liquid dosage forms have not been acceptable due to their lower stability.

The presently-claimed invention solves these problems preparing oral dosage forms containing metformin by providing solid dosage forms comprising particles having a size that is less than 710 microns. According to certain embodiments of the invention, when the particles that make up the oral dosage forms are dispersed in water, the dispersion is homogenous, and no particle resulting from the disintegration of the dosage form has a size larger than 710 microns, as determined by passing the dispersion through a sieve having a nominal mesh size of 710 microns. *See* page 5. According to further embodiments, the particles that result from the disintegration of the dosage form include an internal core comprising the active ingredient and appropriate excipients, and an external layer comprising a sweetening agent and appropriate excipients. *See* page 11. As demonstrated by the data contained in Tables 11 and 12

of the specification, the presently-claimed dosage forms beneficially provide a pharmacokinetic profile that is equivalent to Glucophage®-brand metformin tablets, without any of the drawbacks described above.

Applicants submit that Timmins relates to dosage forms containing dibasic acid salts of metformin as an alternative to metformin hydrochloride, which is said to have an unpleasant taste and is considered problematic from a manufacturing standpoint. The alternative salts have improved taste and handling properties, and are "significantly less soluble in water than the hydrochloride salt and thus provide the opportunity for formulating metformin in controlled release systems." *See* col. 2, lines 38-43. Timmins fails to disclose or suggest the preparation of dispersible or orodispersible dosage forms, as claimed and as defined at page 4 of the present specification. Timmins provides no disclosure to enable one skilled in the art to prepare such a dosage form.

Timmins discloses at column 6, lines 2-3, that the medicament(s) and optional fillers are mixed and passed through a #12 to #40 mesh screen (425 microns to 1.7 mm), followed by adding optional filler/binder, a disintegrant, and a lubricant, and then mixing and compressing the mixture. The Office Action takes the position that this disclosure renders the size feature of the presently-claimed invention obvious, but Applicants respectfully disagree. Although the active ingredient is sieved in Timmins, the steps of adding additional excipients to the sieved active ingredient, followed by mixing and compressing, Applicants submit that this process will result in a mixture containing particles that are larger than 710 microns.

Applicants submit the presently-claimed invention specifically relates to pharmaceutical compositions comprising particles having a size that is less than 710

microns, where the particles comprise the various components set forth in the claims. Further, according to some embodiments, the metformin used in the presently-claimed invention preferably has a grain size of less than 100 microns, which is far smaller than the grain size for the active ingredients disclosed in Timmins. *See* page 8 of the present specification.

Balkan fails to remedy these deficiencies of Timmins with respect to the presently-claimed invention, because although it discloses combinations of DDP-IV inhibitors and an antidiabetic compound such as metformin, it utterly fails to disclose or suggest dispersible or orodispersible pharmaceutical compositions, or dosage forms that include particles having a size that is less than 710 microns.

Accordingly, because the combination of Timmins and Balkan fails to disclose or suggest at least these features of the presently-claimed invention, no *prima facie* case of obviousness has been established. In view of the amendments and remarks presented above, Applicants submit that claims 1-26 and 28 are not unpatentable over any combination of Timmins and/or Balkan, and respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

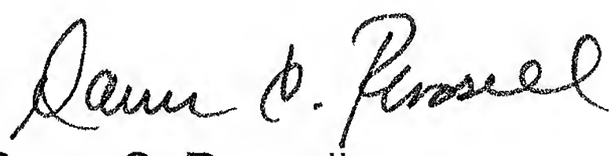
CONCLUSION

In view of the foregoing, Applicants respectfully request reconsideration of the application, withdrawal of the outstanding rejections, allowance of Claims 1-26 and 28-31, and the prompt issuance of a Notice of Allowability.

Should the Examiner believe anything further is desirable in order to place this application in better condition for allowance, the Examiner is requested to contact the undersigned at the telephone number listed below.

In the event this paper is not considered to be timely filed, the Applicants respectfully petition for an appropriate extension of time. Any fees for such an extension, together with any additional fees that may be due with respect to this paper, may be charged to counsel's Deposit Account No. 01-2300, referencing attorney docket number 030363.00003.

Respectfully submitted,



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